Non-classical sources of tumour specific antigen in checkpoint inhibitor response

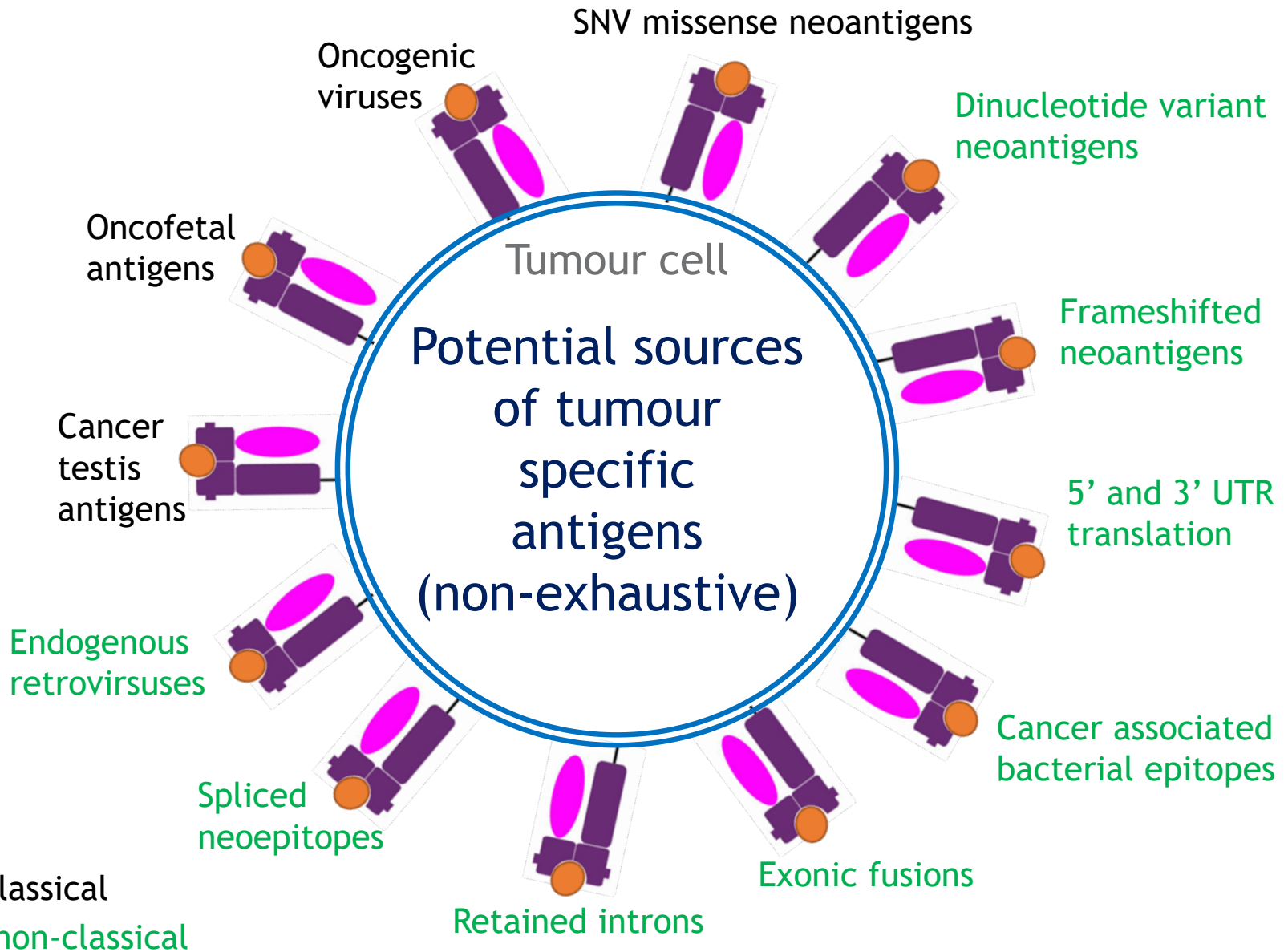
Workshop Lund 2022.

4th May 2022

Dr Kevin Litchfield

Sources of tumour specific antigen

https://www.ucl.ac.uk/cancer/tigi-lab



Black is categorised as classical

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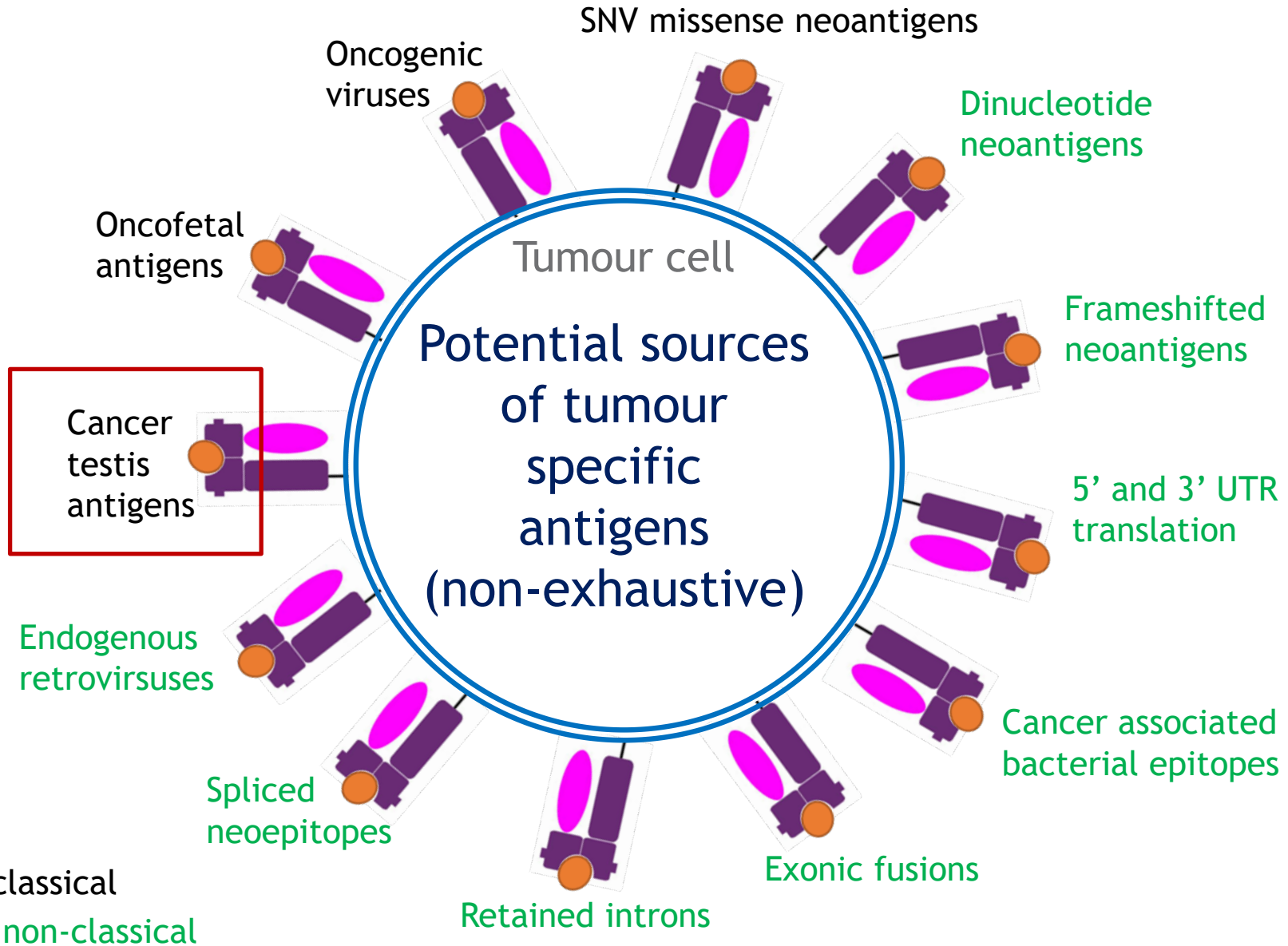

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Cancer/testis antigens

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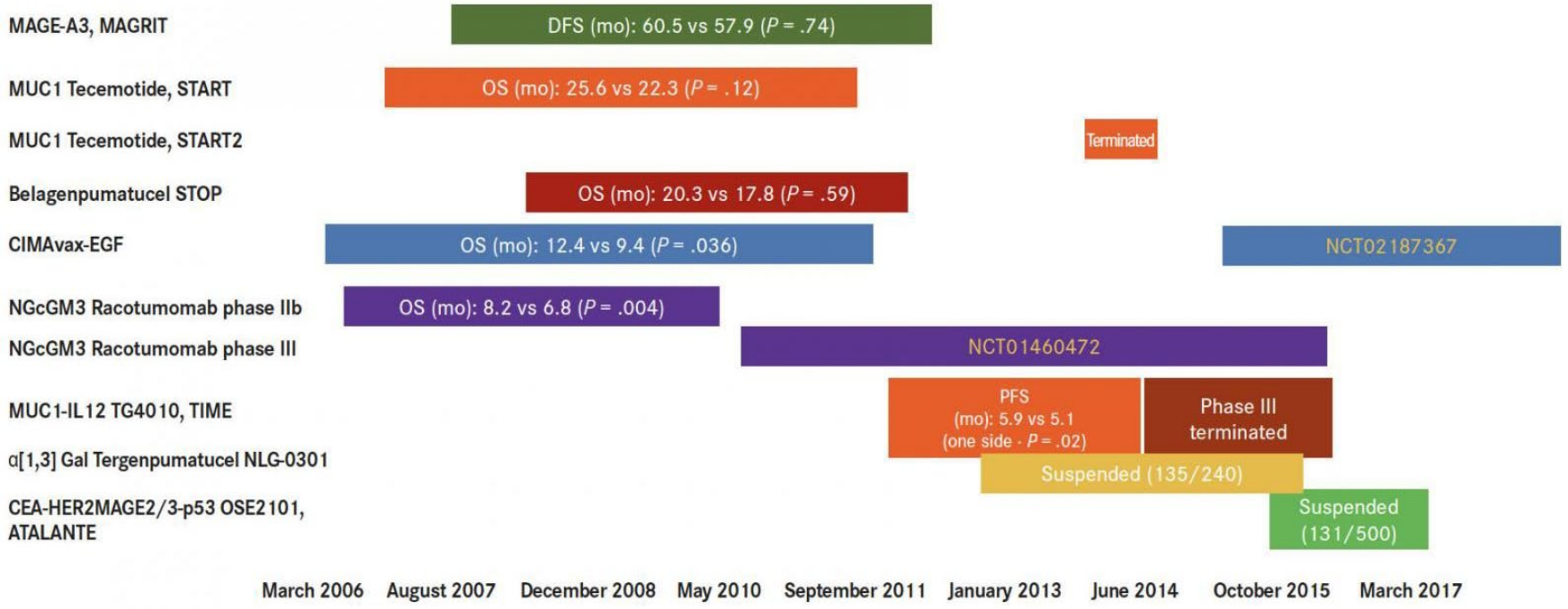

Dy et al., The Journal of Targeted Therapies in Cancer, 2018 April, Volume 7, Issue 2

- A lot of cancer/testis antigen vaccine trials have been negative
- Unclear if this is because they are poorly immunogenic targets (i.e. some degree of self tolerance) or whether therapeutic vaccines are ineffective
- Many of these targets are now under development as T cell therapies

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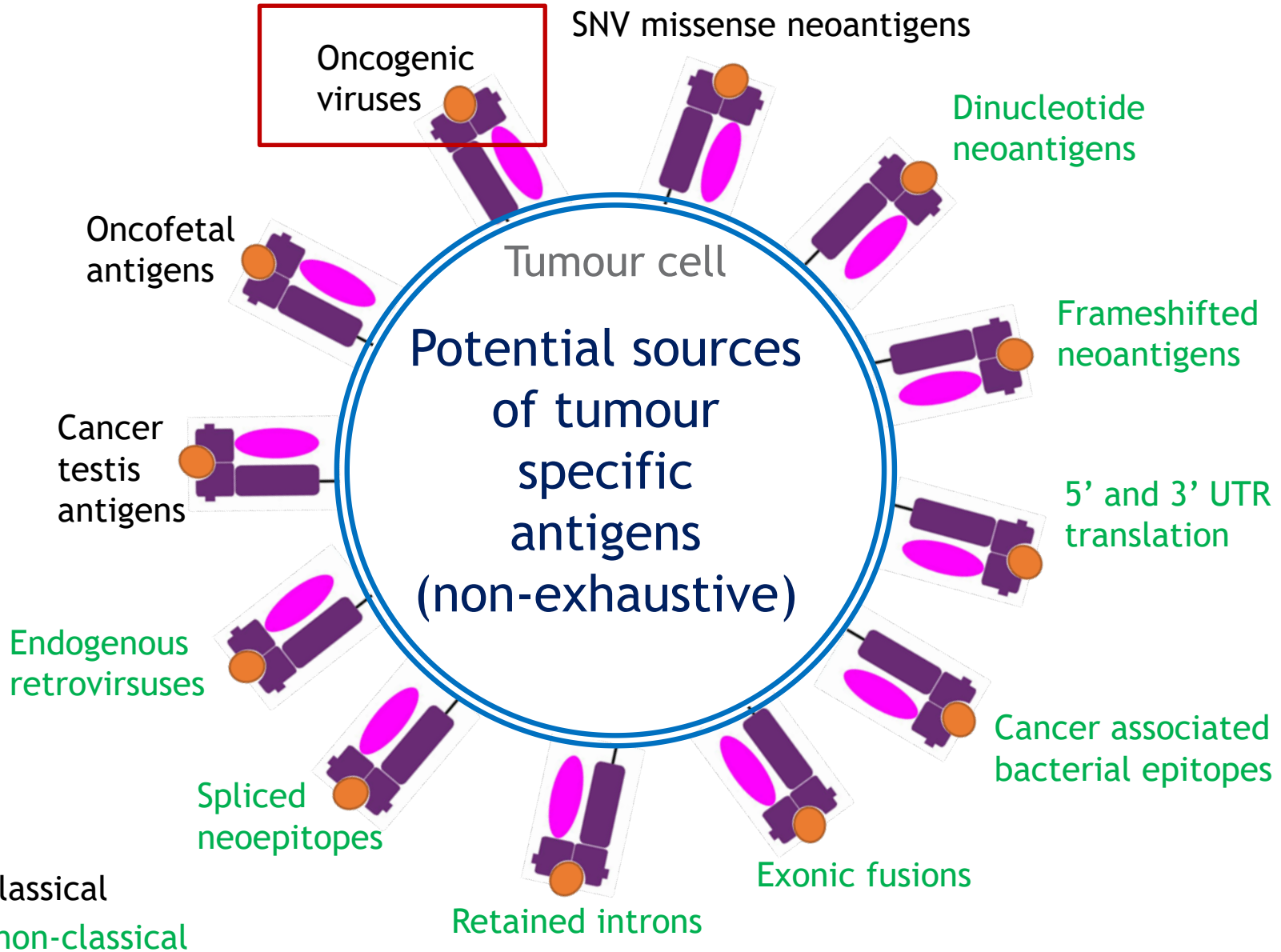

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Oncogenic viruses are classically immunogenic

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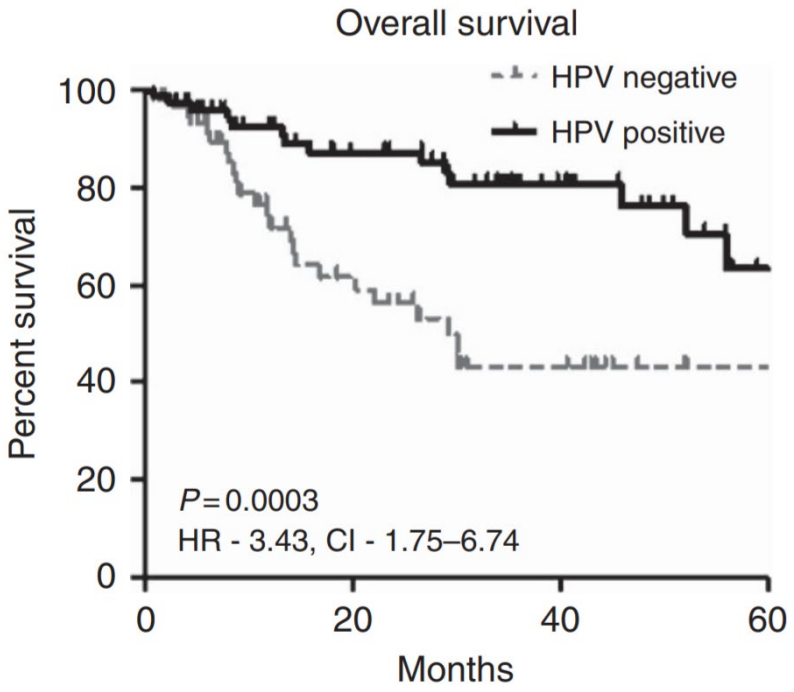

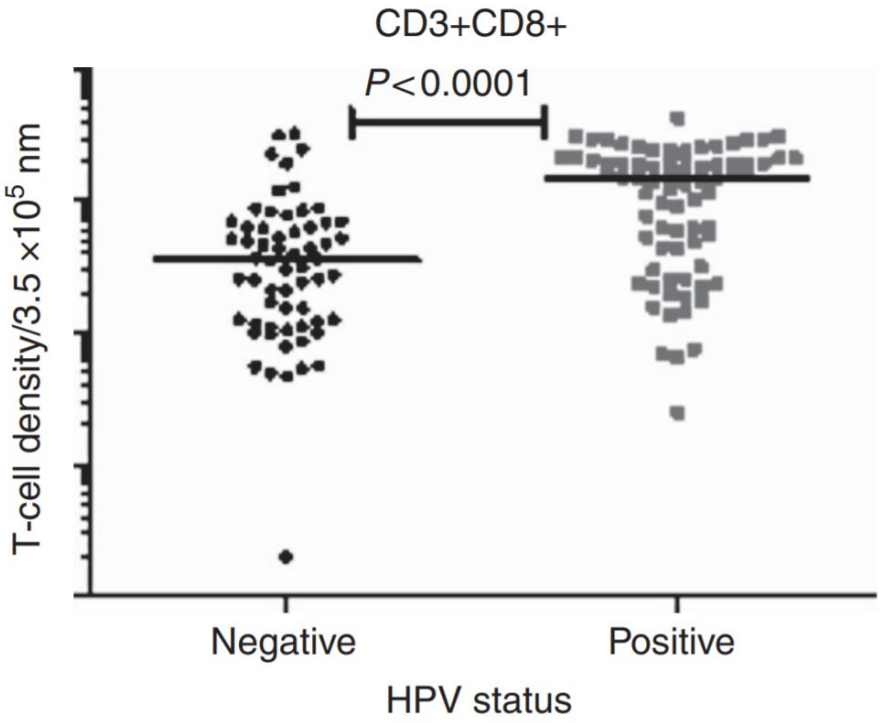

Oguejiofor et al. 2015

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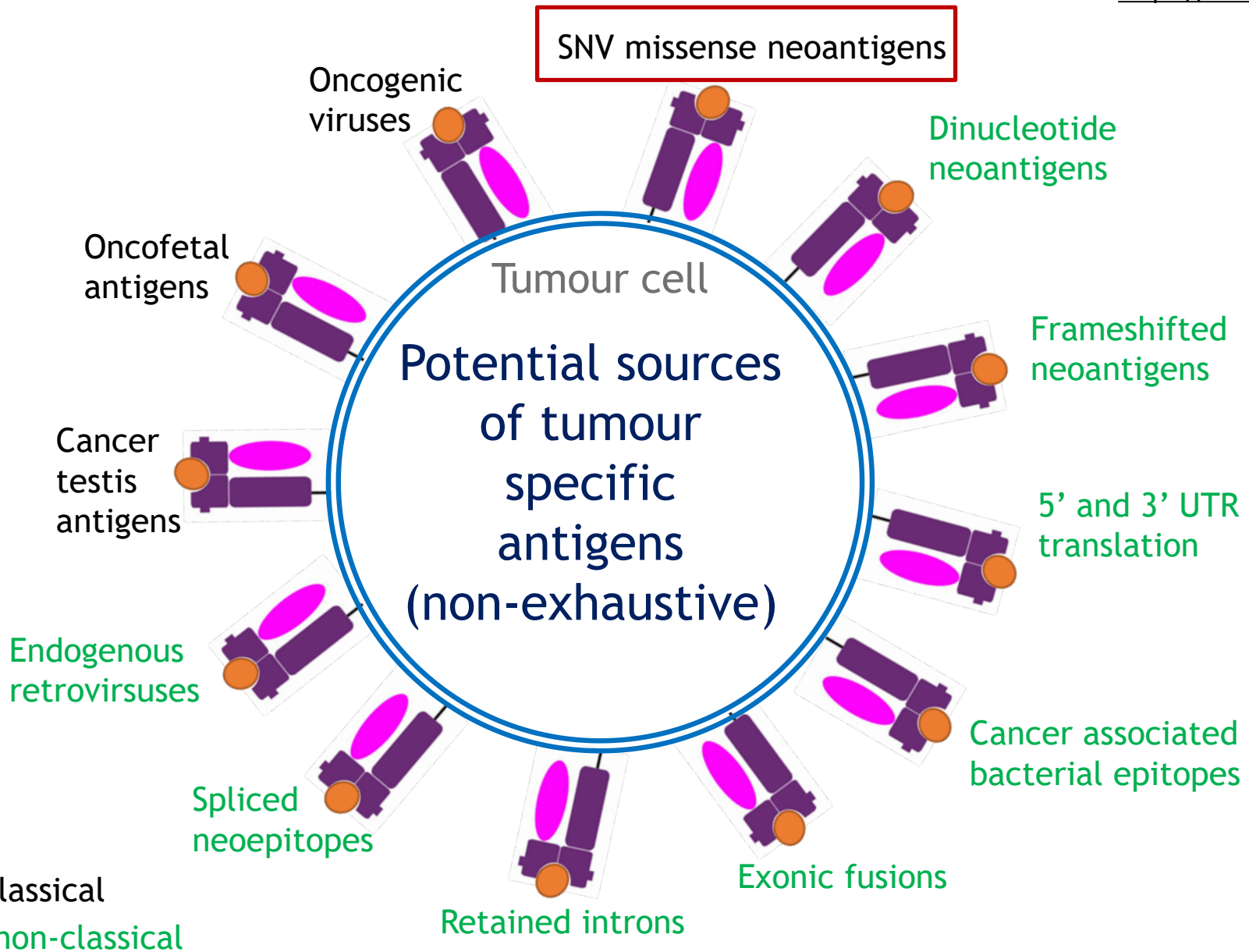

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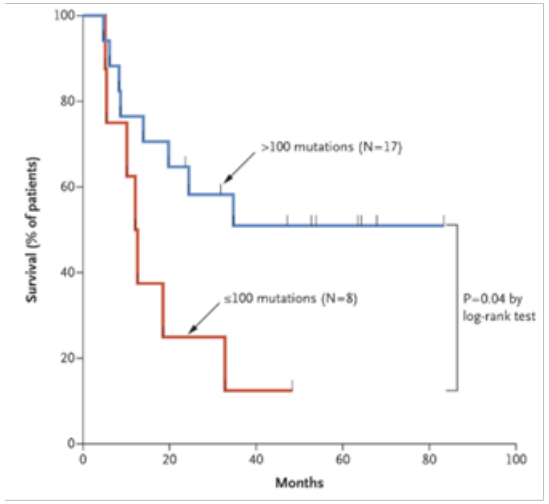
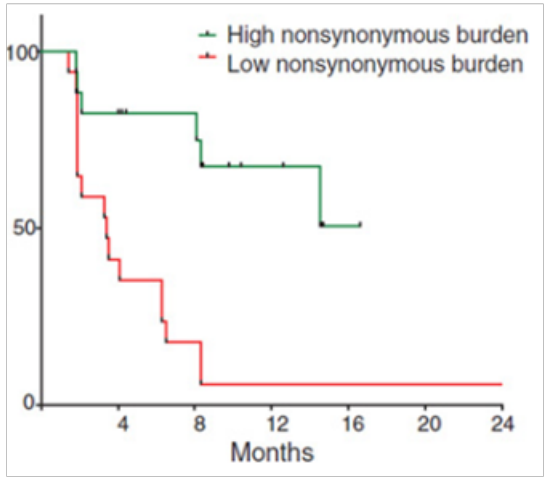
SNV missense neoantigens predict IO response

Melanoma:



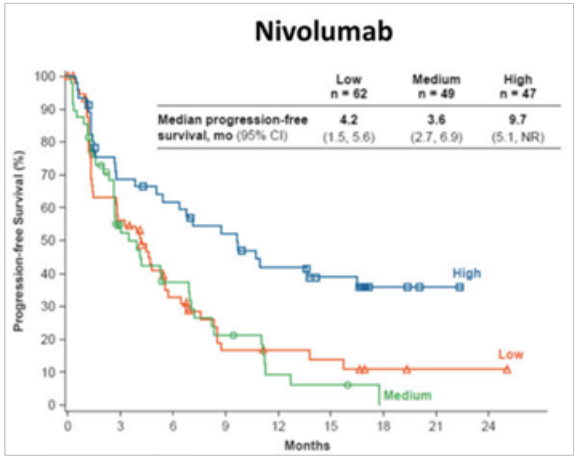
Snyder et al. 2015

NSCLC:



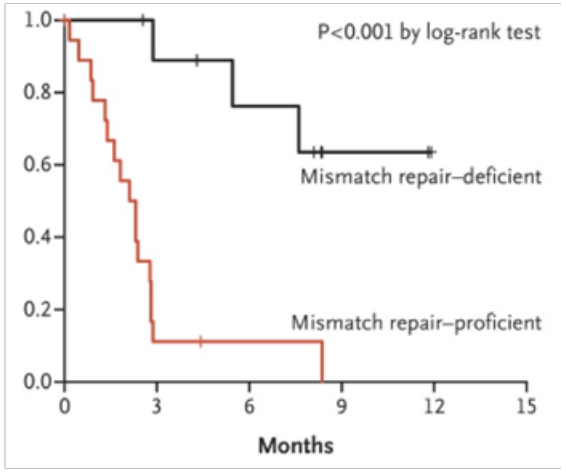
Rizvi et al. 2015

Bladder:

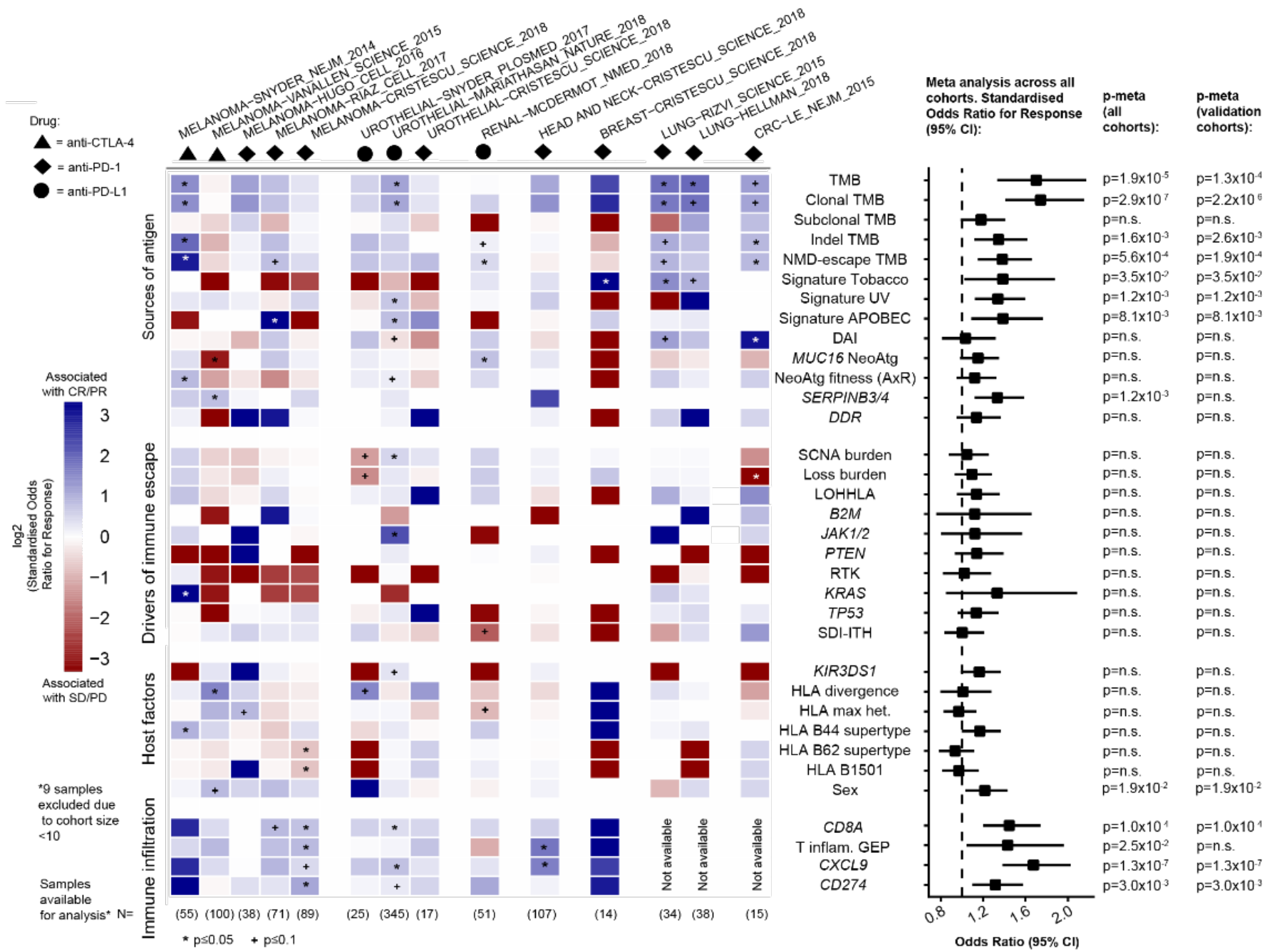


Aggen et al. 2017

CRC:



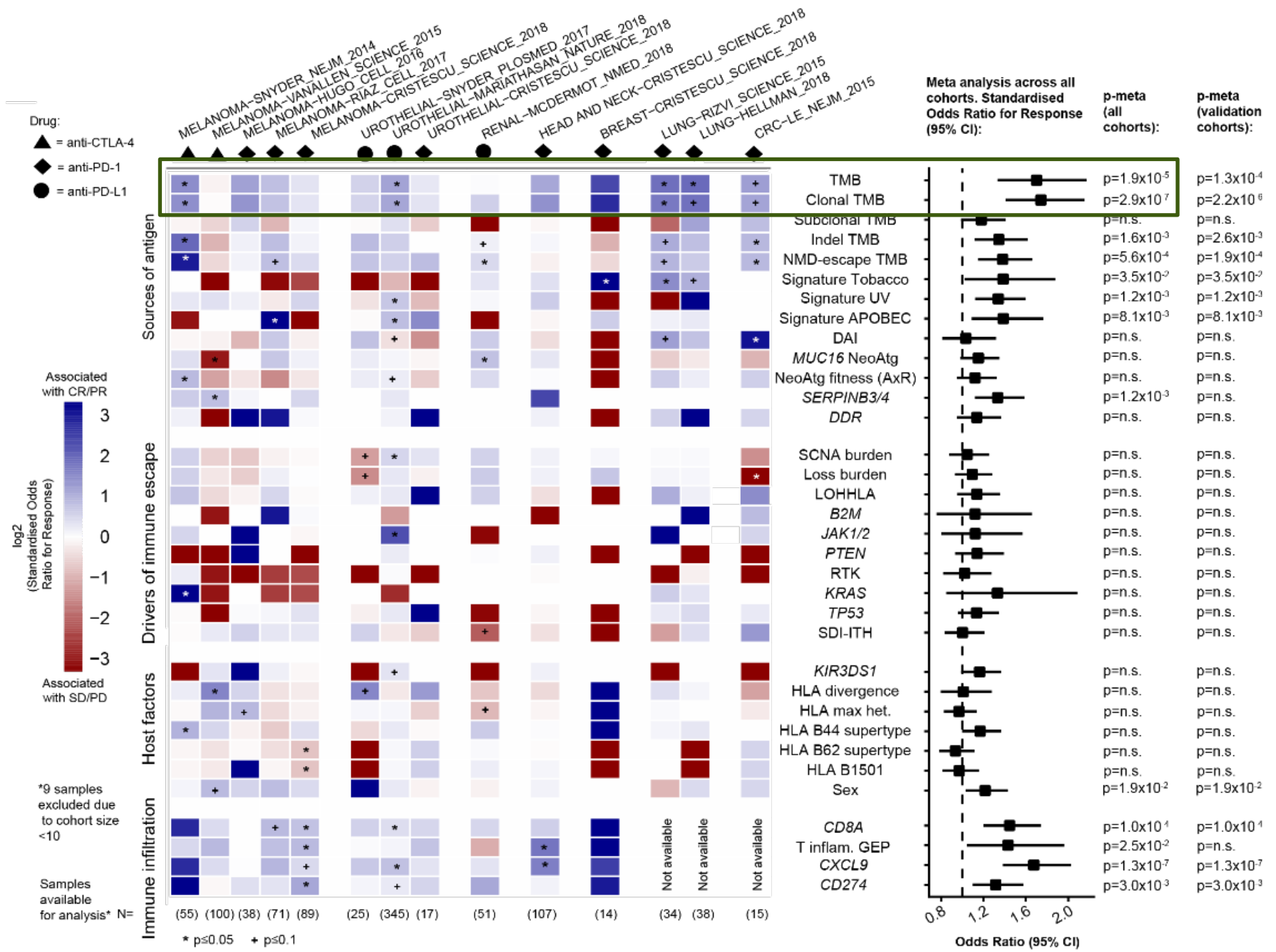
Dung et al. 2015



https://www.ucl.ac.uk/cancer/tigi-lab

- Meta-analysis of >1000 checkpoint inhibitor (CPI) treated patients
- TMB the strongest predictor of CPI response

Litchfield*, Reading* … McGranahan#, Quezada#, Swanton#. (2021 Cell)



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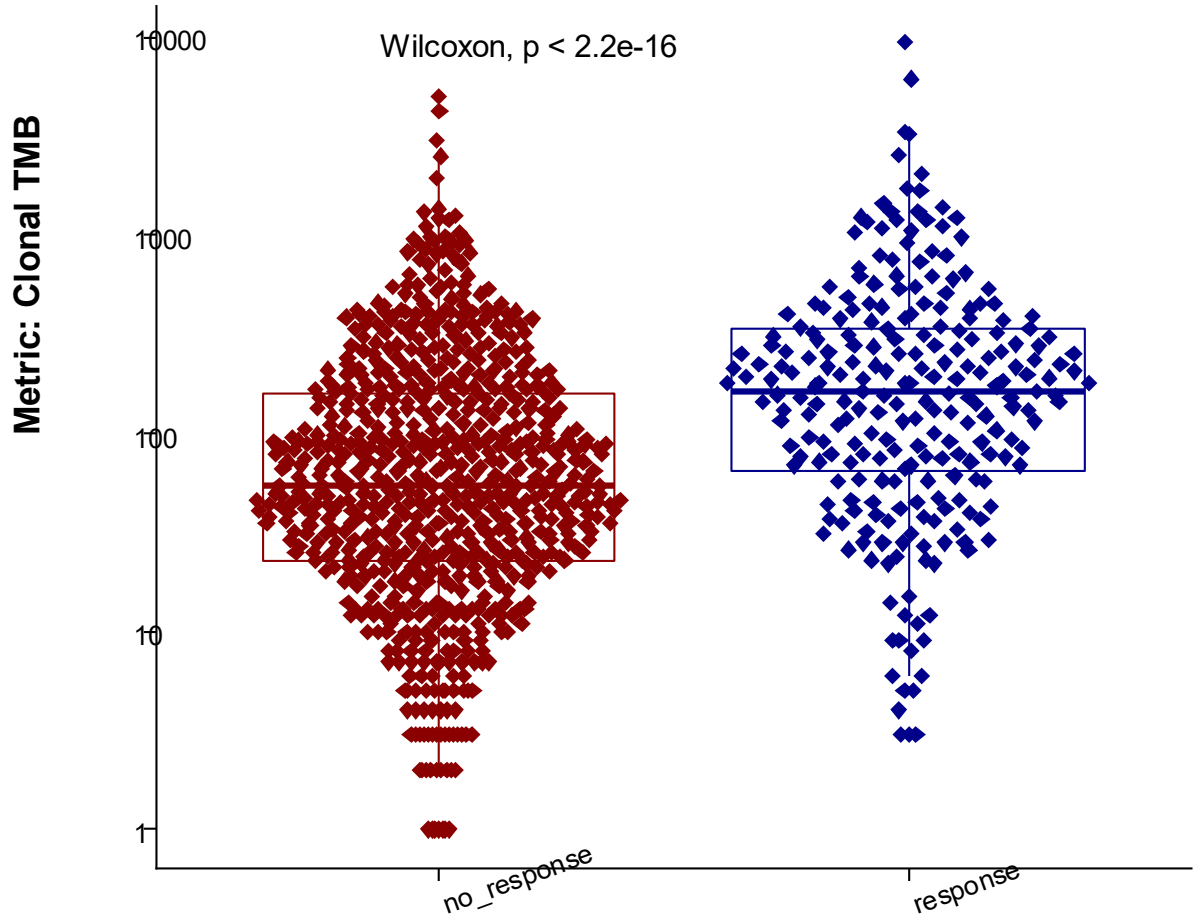
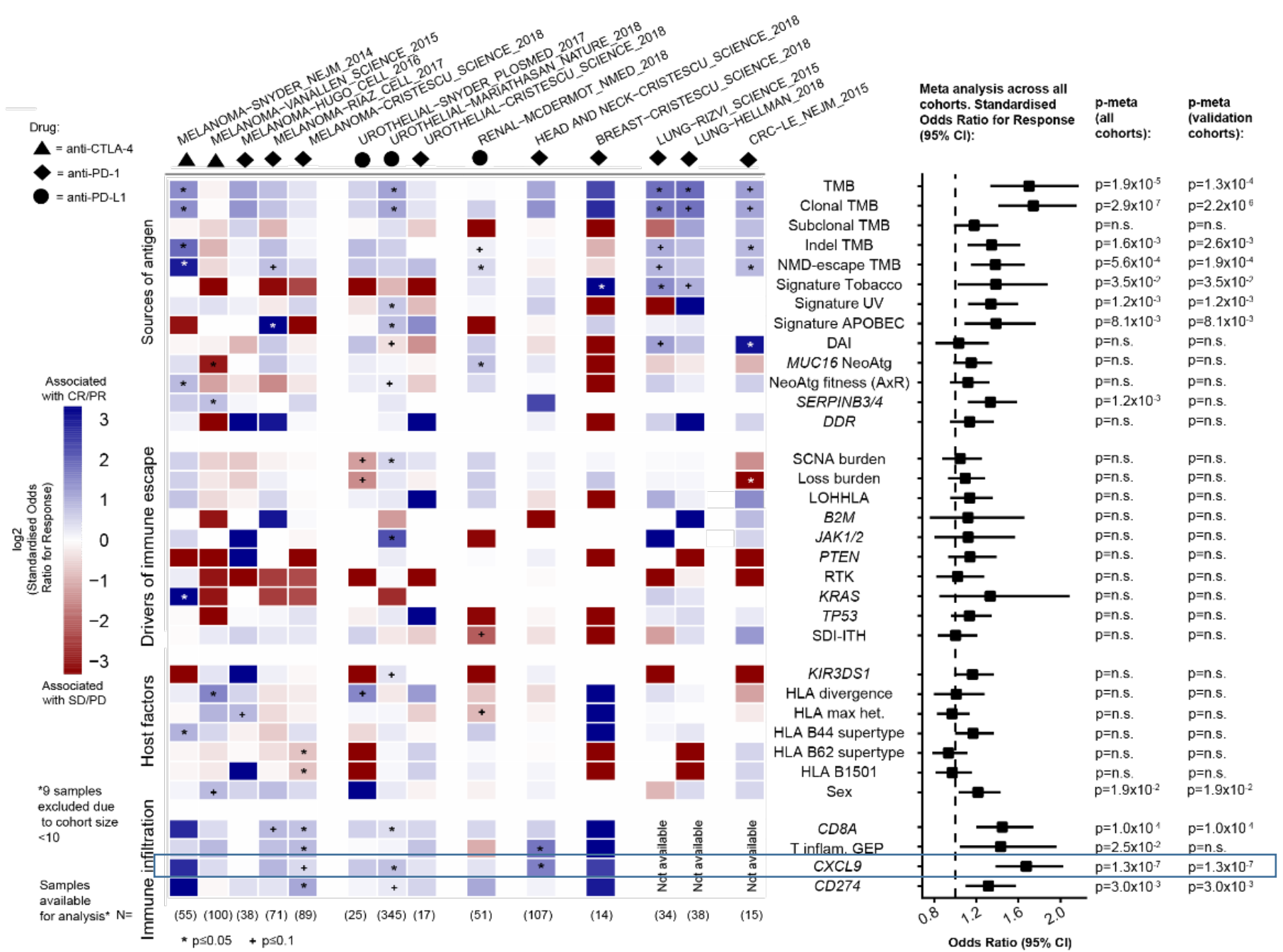
Clonal TMB

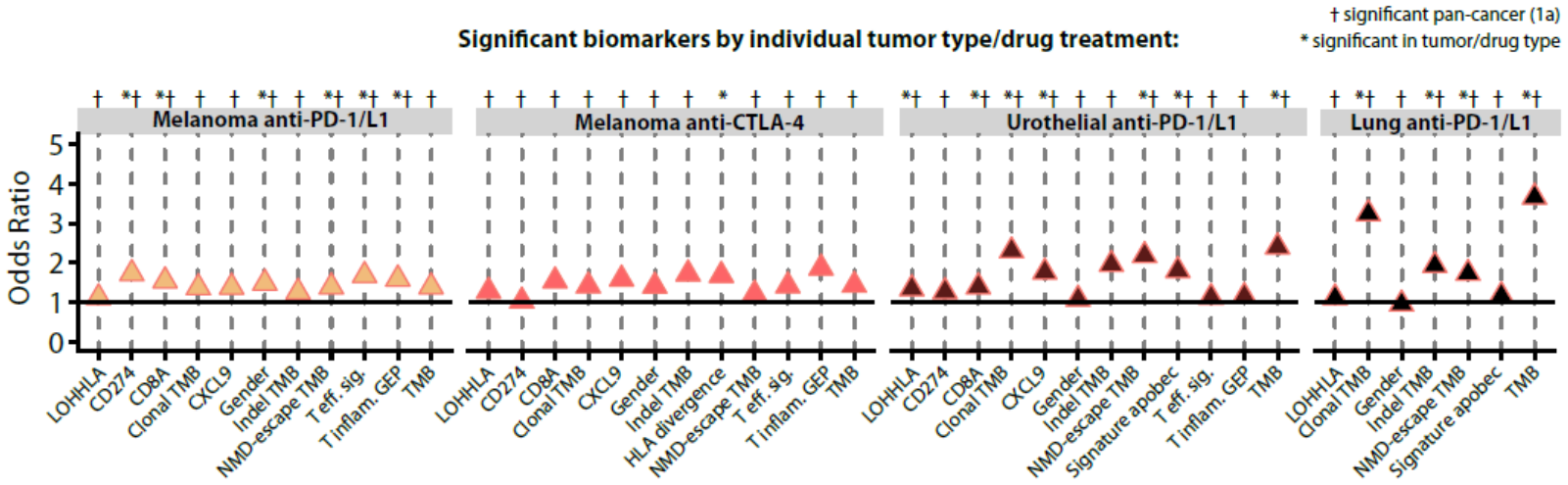


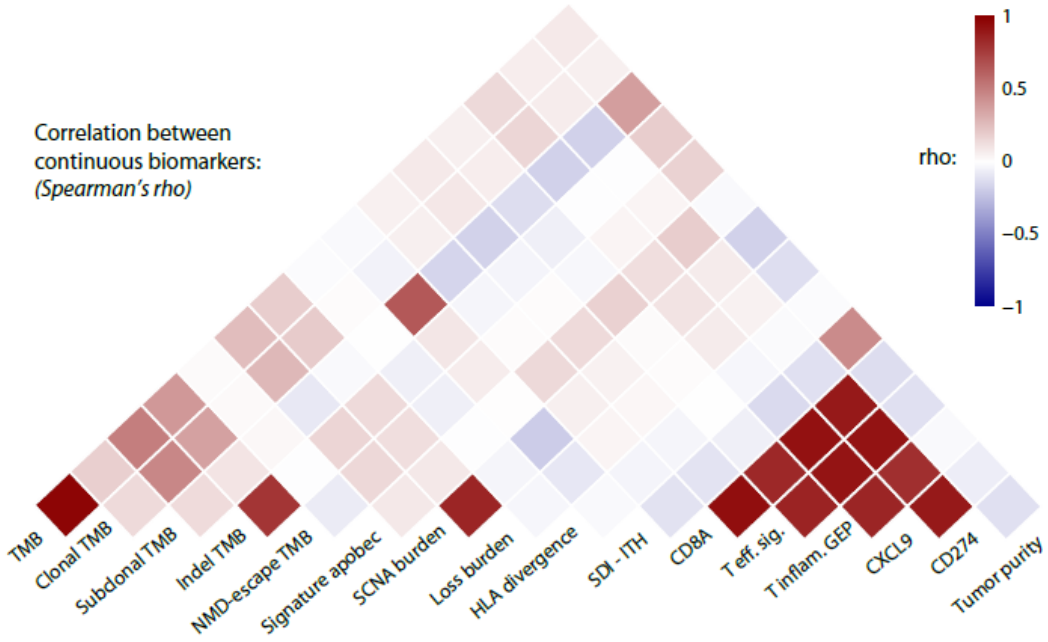
- Clonal TMB strongest predictor of CPI response
- Responders have ~100 additional Clonal mutations



Litchfield et al. 2021 (Cell)

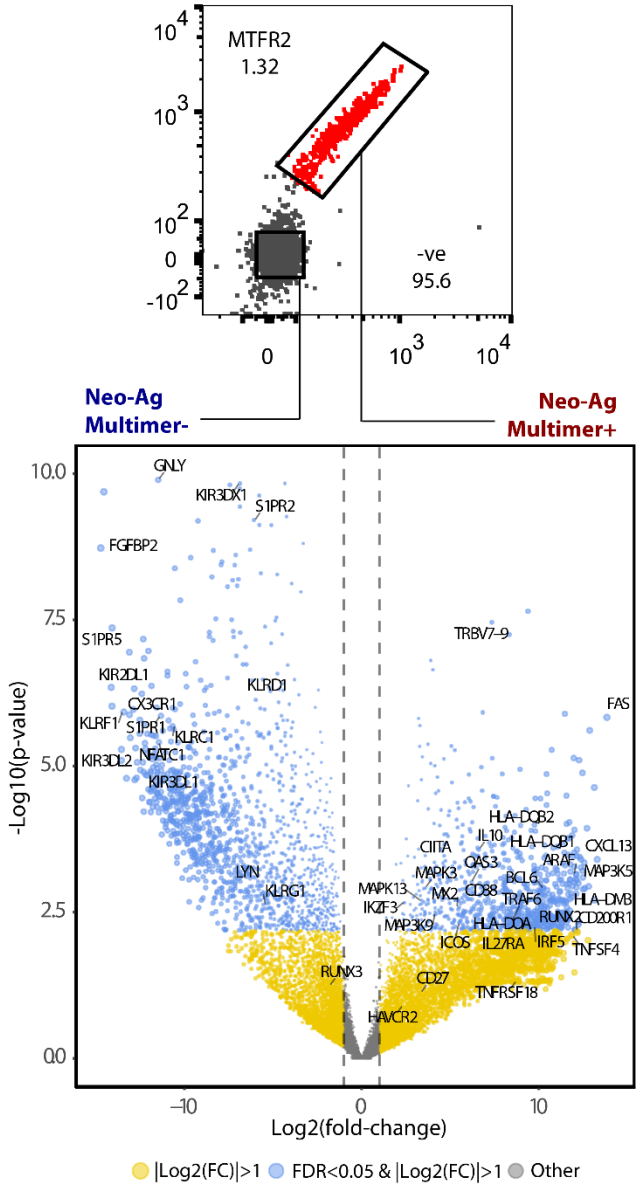
Break down by cancer/drug type and correlation between markers



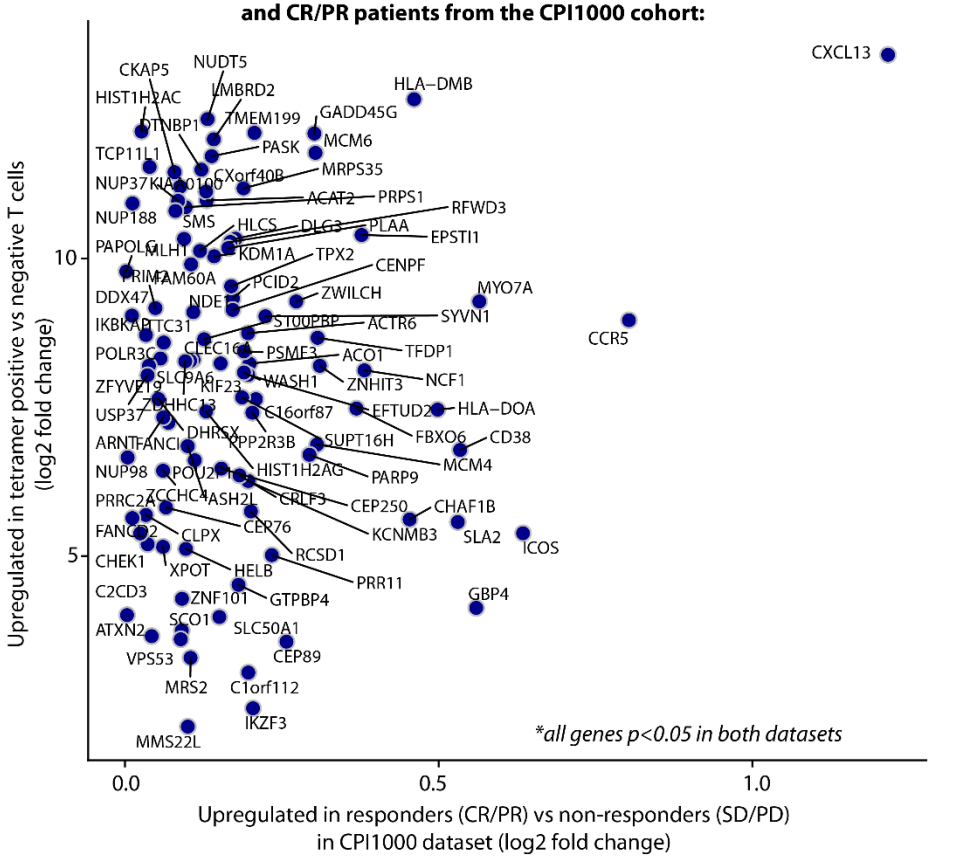


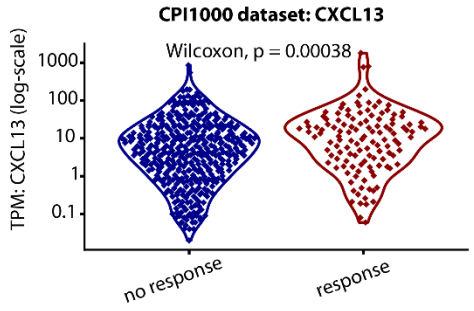
Tetramer sorted single cell RNAseq:

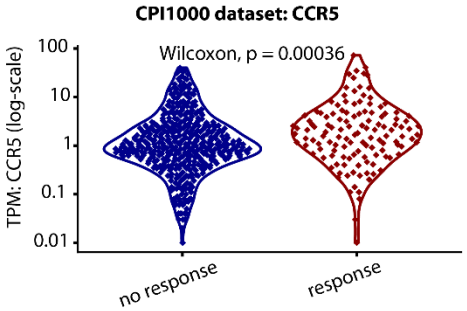
CD8 TILs from NSCLC case L011, multimer sorted for reactivity to clonal neoantigen and single cell RNA sequenced:



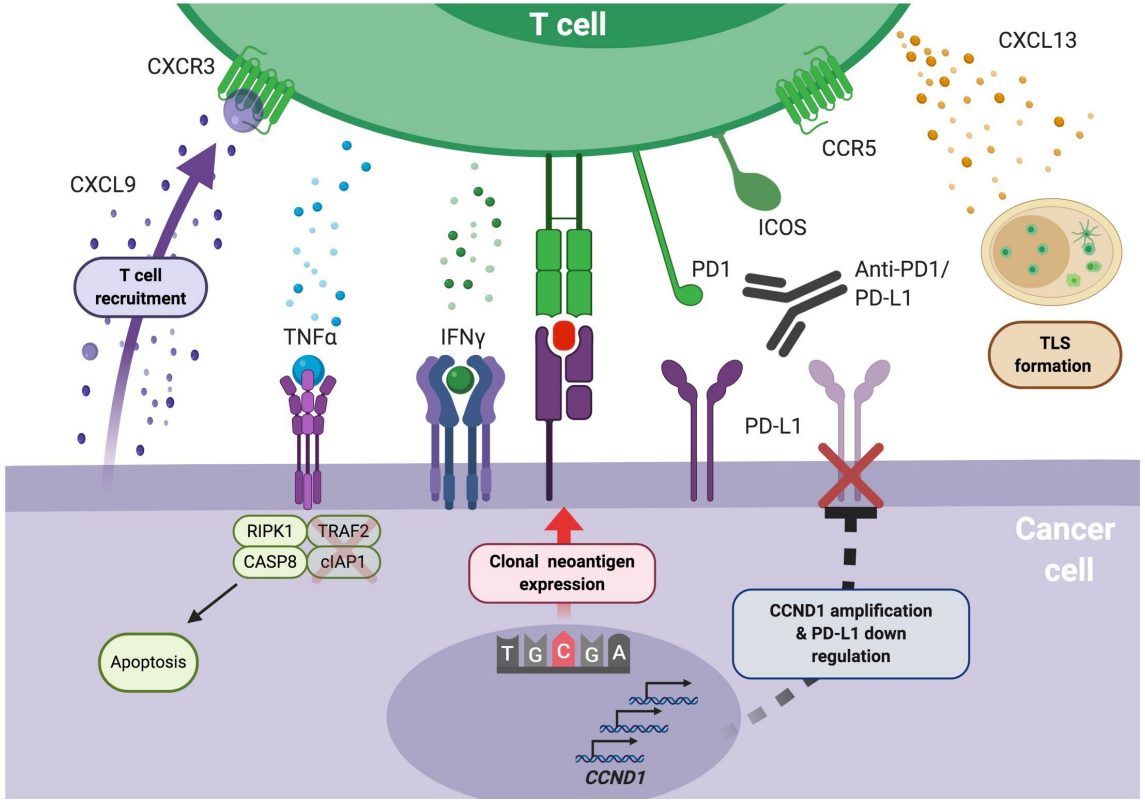
Genes up-regulated in both multimer +ve CD8 TILs and CR/PR patients from the CPI1000 cohort:

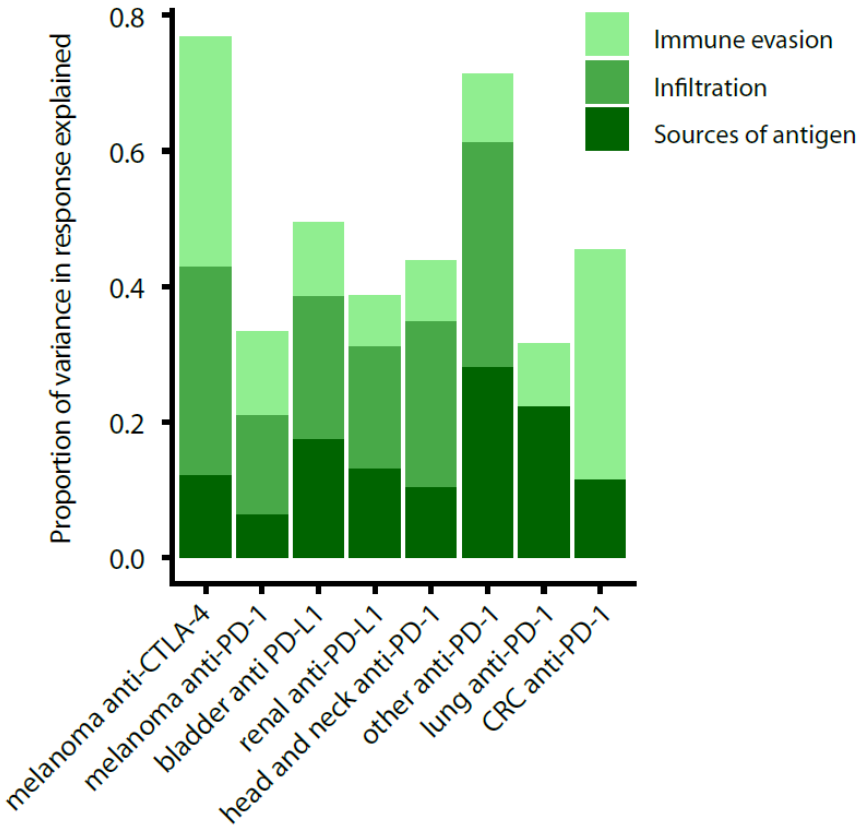






We understand a subset of the factors influencing CPI response, but what >50% of the explanation is still missing.





What is missing?

Litchfield et al. 2021 (Cell)

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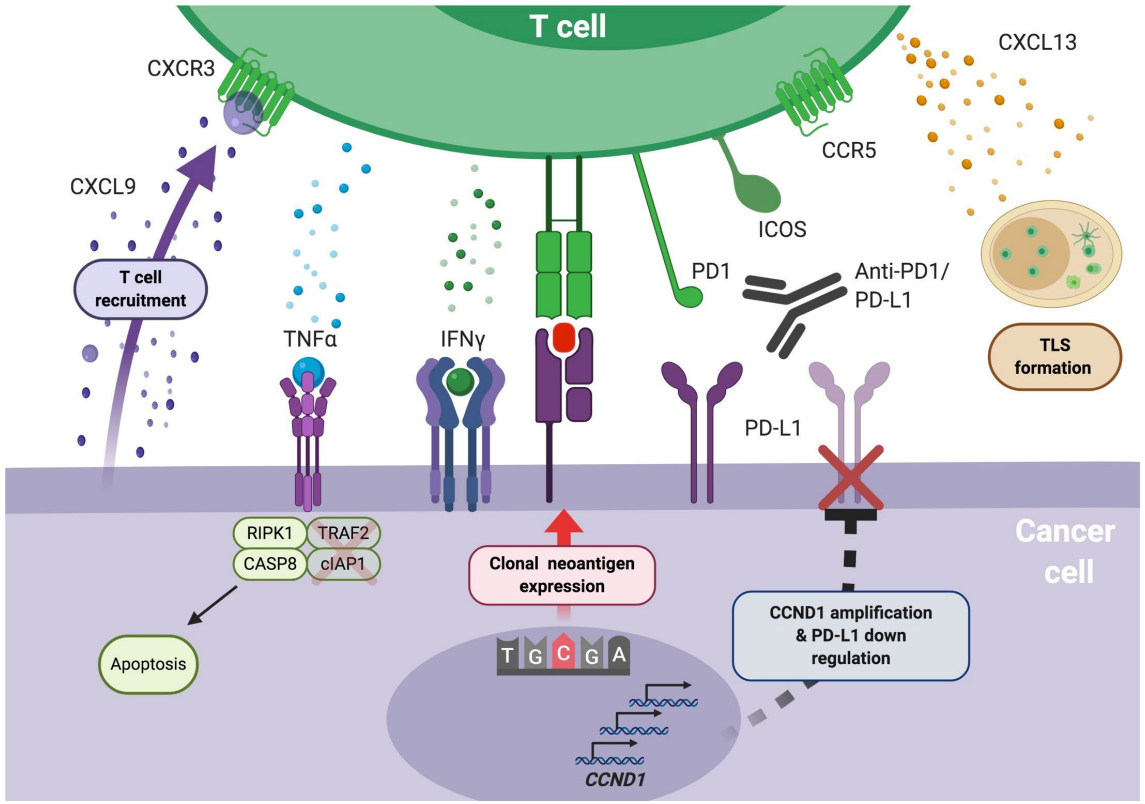

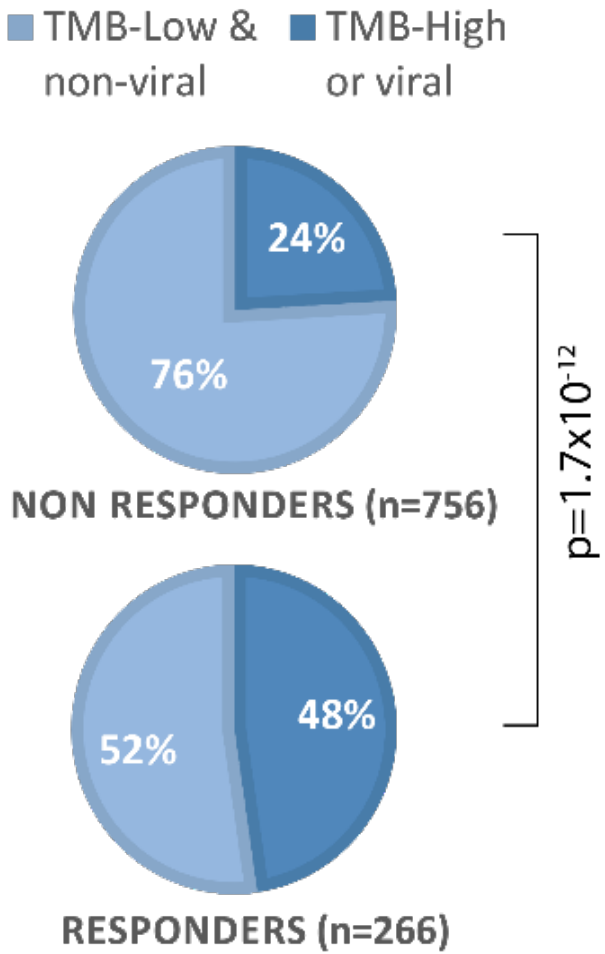

What is missing?

Data from Litchfield et al. 2021

Litchfield et al. 2021 (Cell)

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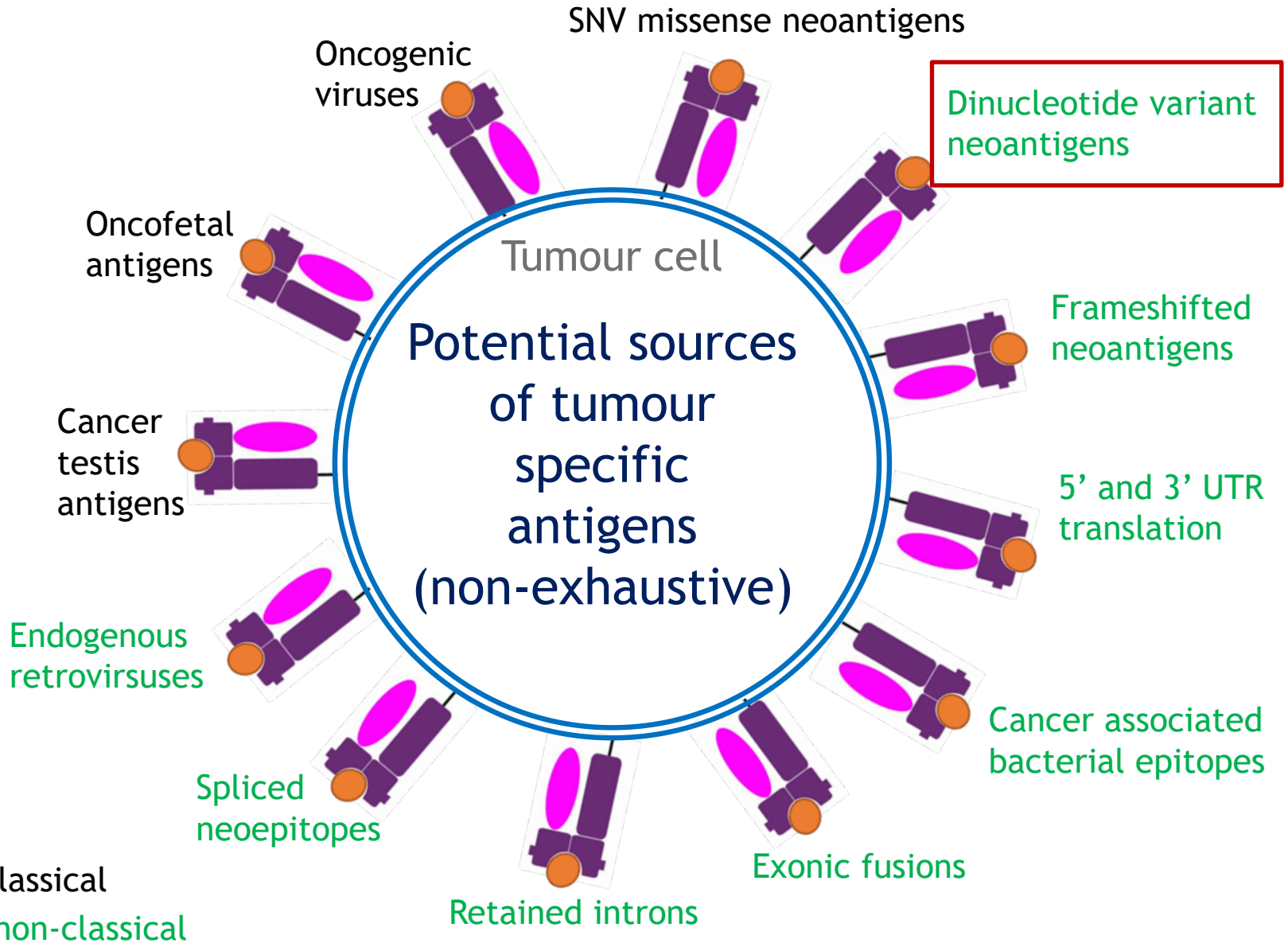

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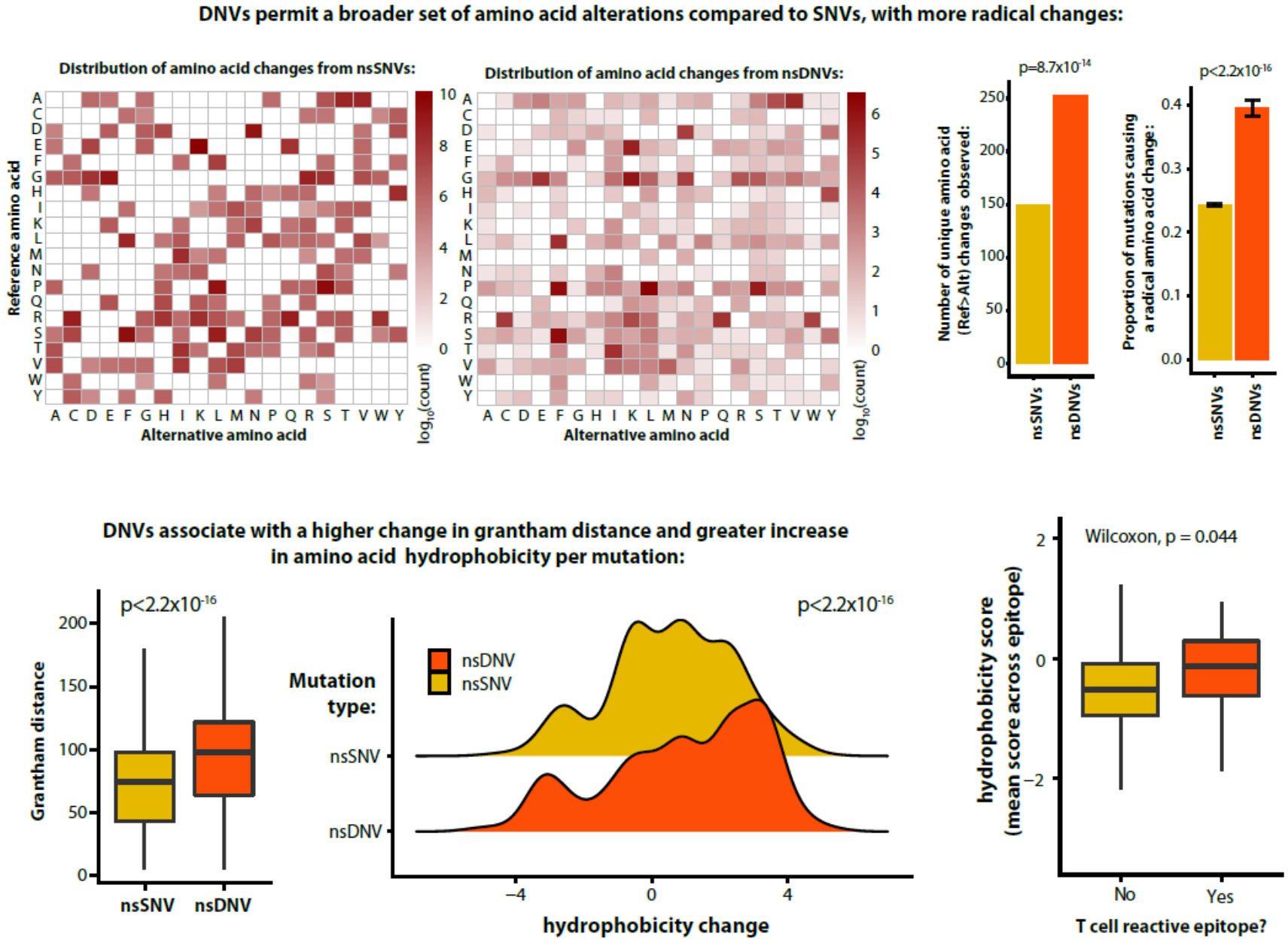

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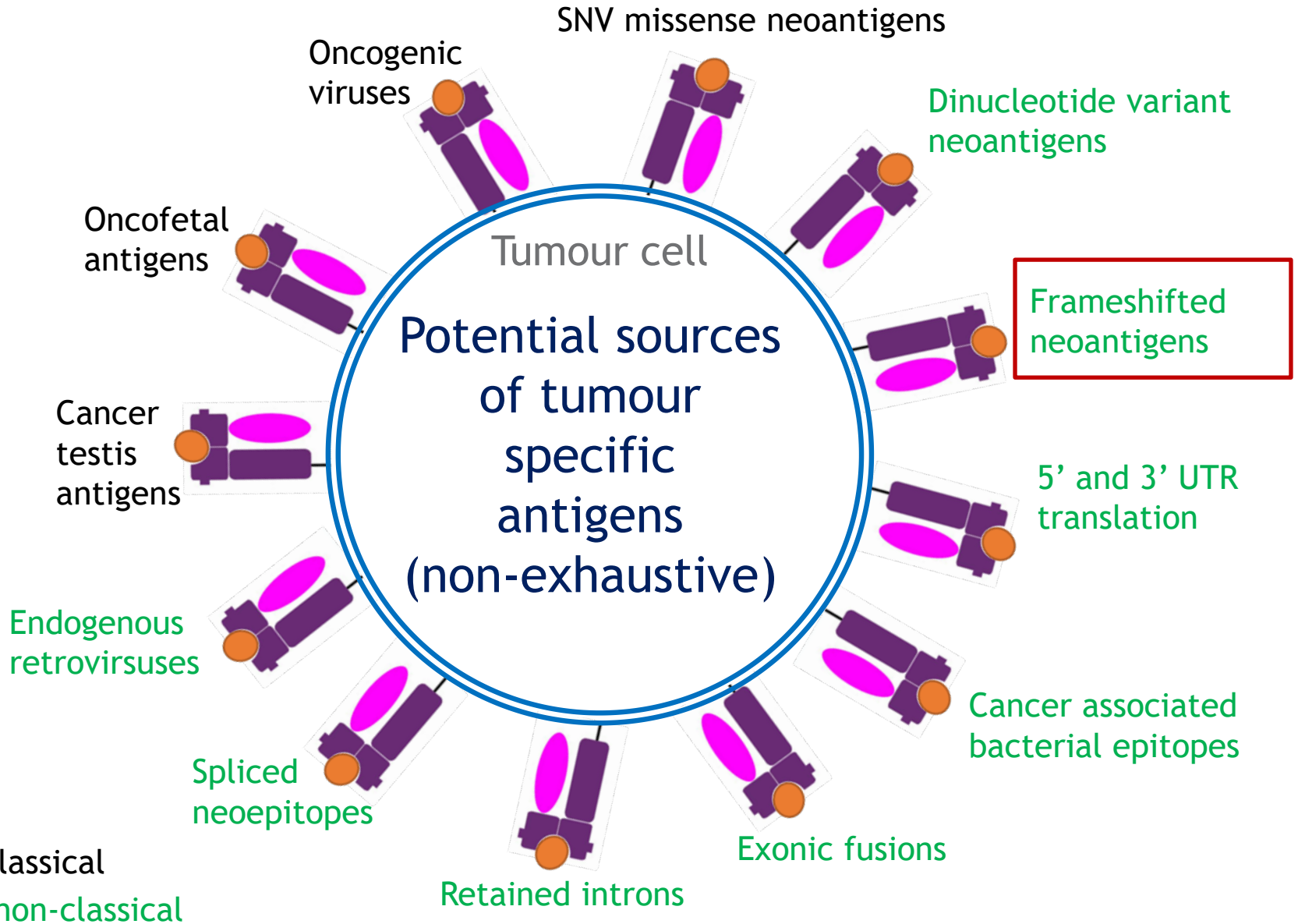

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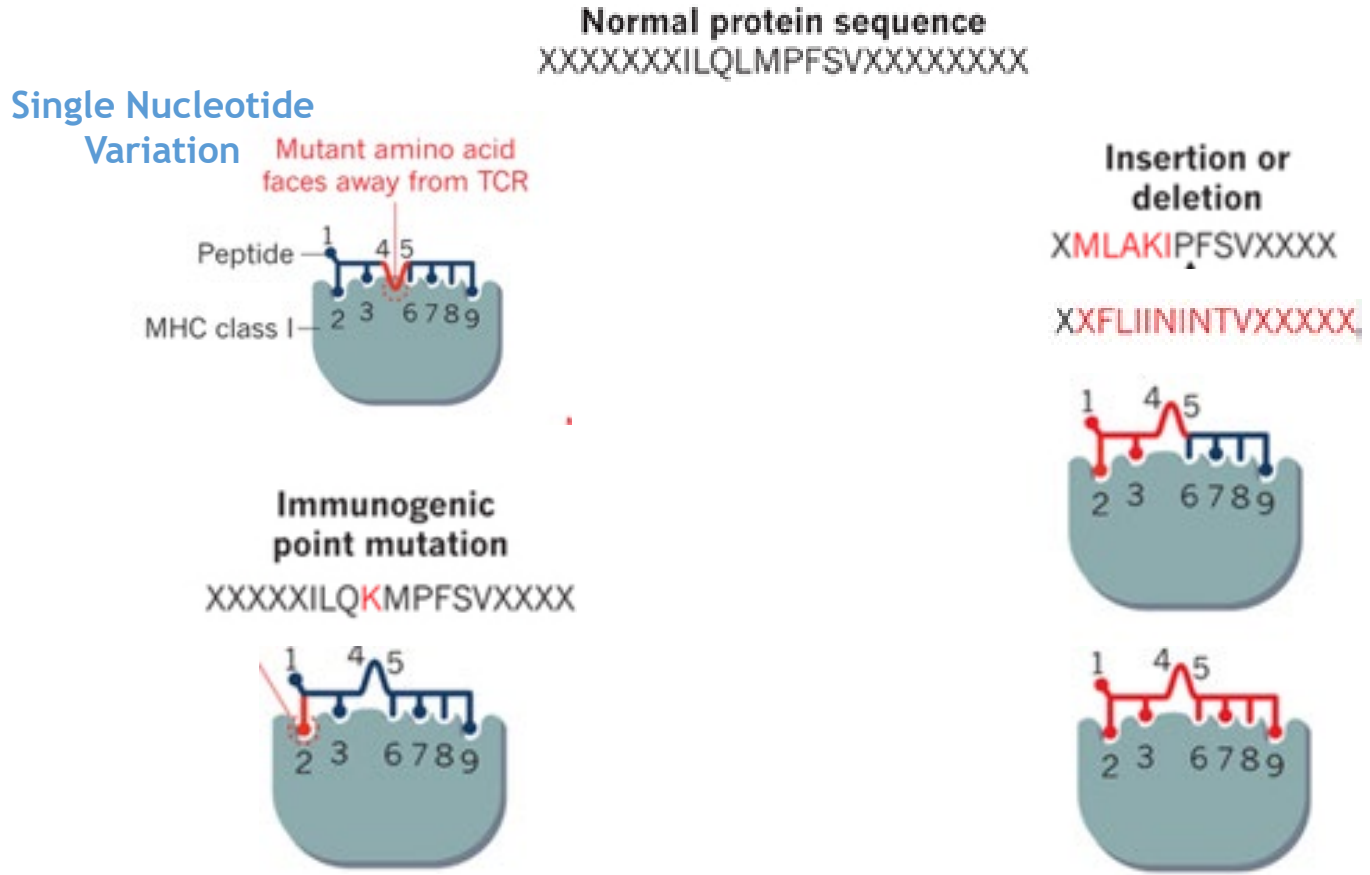
Frameshift indels – only ~5% of all mutations, but highly immunogenic



Chen & Mellman,
Nature (Review) 2017

	Neoantigens per mutation	Mutant-specific neoantigens per mutation
nsSNVs	0·64	0·22
fs-indels	2·00	2·00
Enrichment	3·13	8·94

Turajlic, Litchfield et al.
Lancet Oncology 2017

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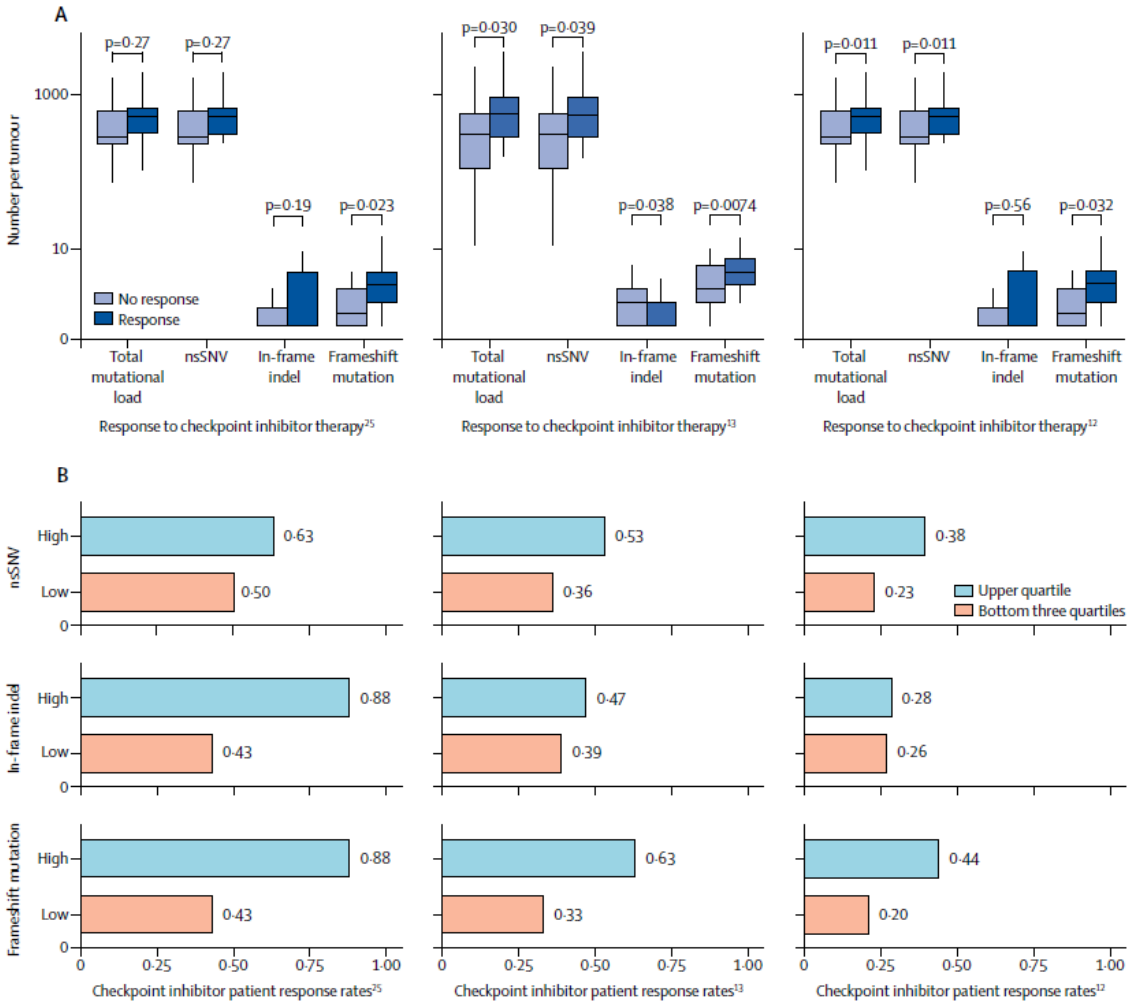


Turajlic, Litchfield et al. Lancet Oncology 2017

Further data to support indels as a biomarker across other studies:

JCI insight

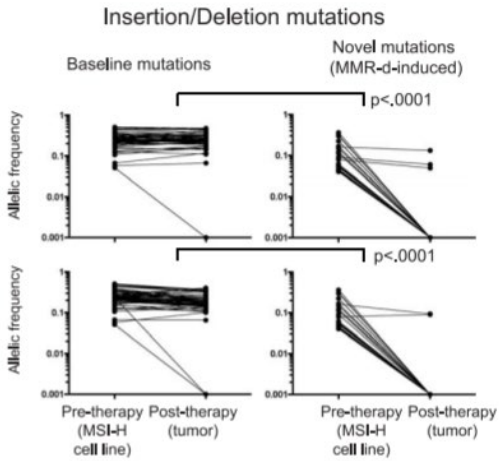
RESEARCH ARTICLE

Frameshift events predict anti–PD-1/L1 response in head and neck cancer

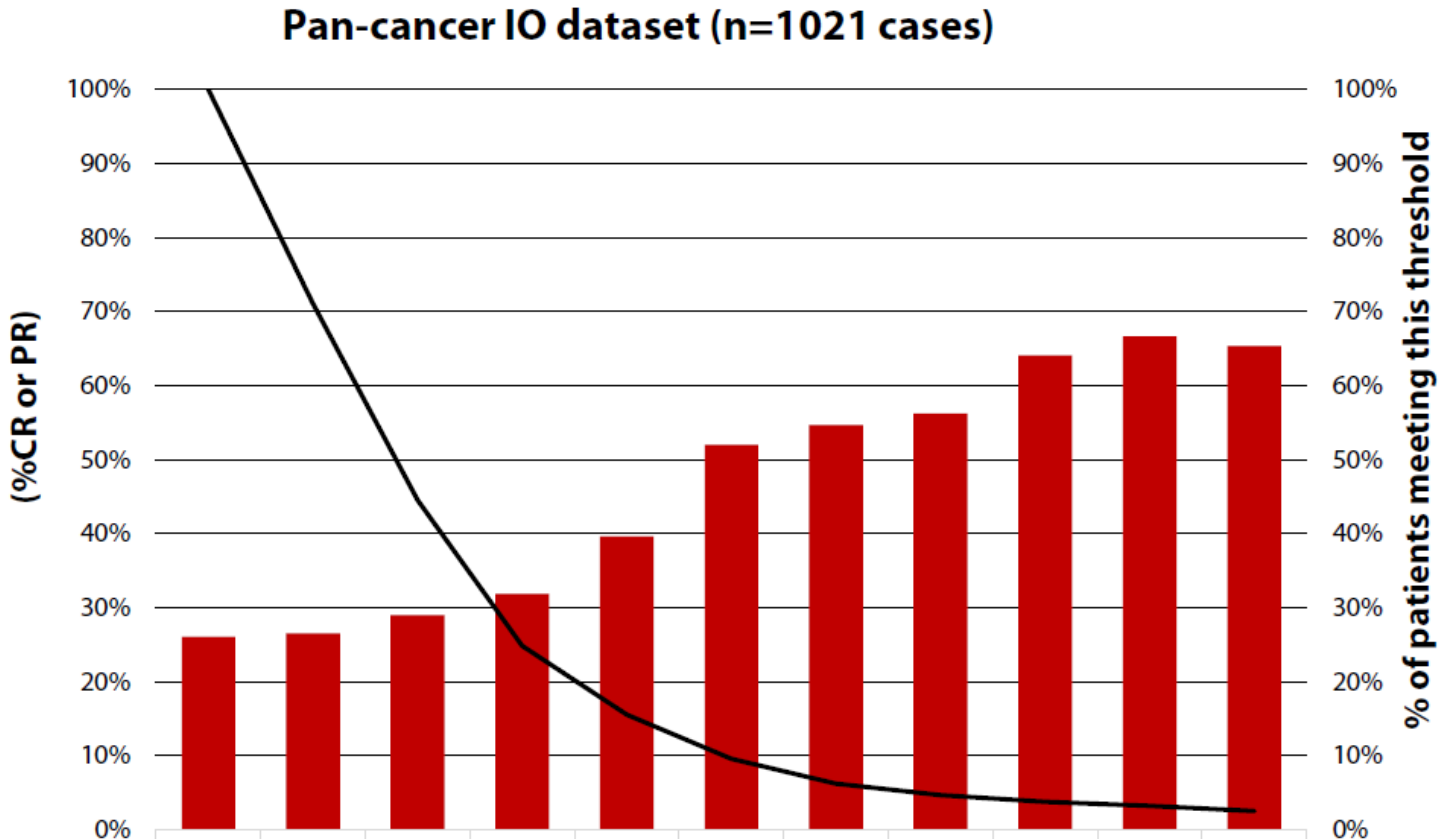
Genetic diversity of tumors with mismatch repair deficiency influences anti–PD-1 immunotherapy response

Dung T. Le[2,6,9], Luis A. Diaz Jr.[5,12], Timothy A. Chan[3,4,5]‡

response to PD-1 blockade immunotherapy in MMR-d human and mouse tumors. The extent of response is particularly associated with the accumulation of insertion-deletion (indel) mutational load. This study provides a rationale for the genome-wide



Further validated in larger cohorts of >1000 patients

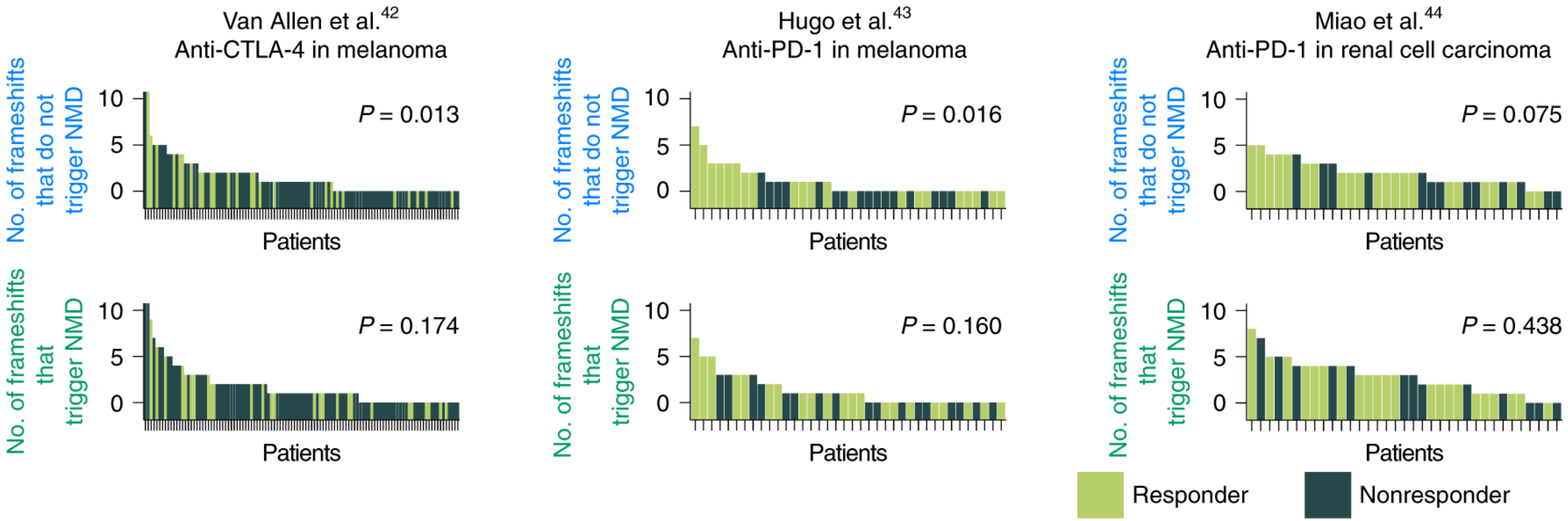


	NMD-escape >= 0	NMD-escape >= 1	NMD-escape >= 2	NMD-escape >= 3	NMD-escape >= 4	NMD-escape >= 5	NMD-escape >= 6	NMD-escape >= 7	NMD-escape >= 8	NMD-escape >= 9	NMD-escape >= 10
Non-Responders (N)	755	533	323	173	96	47	29	21	14	11	9
Responders (N)	266	193	132	81	63	51	35	27	25	22	17
% of patients hitting threshold	100%	71%	45%	25%	16%	10%	6%	5%	4%	3%	3%

Litchfield et al. 2020 (Nature Communications).

Litchfield et al. 2021 (Cell).

Same results validated independently



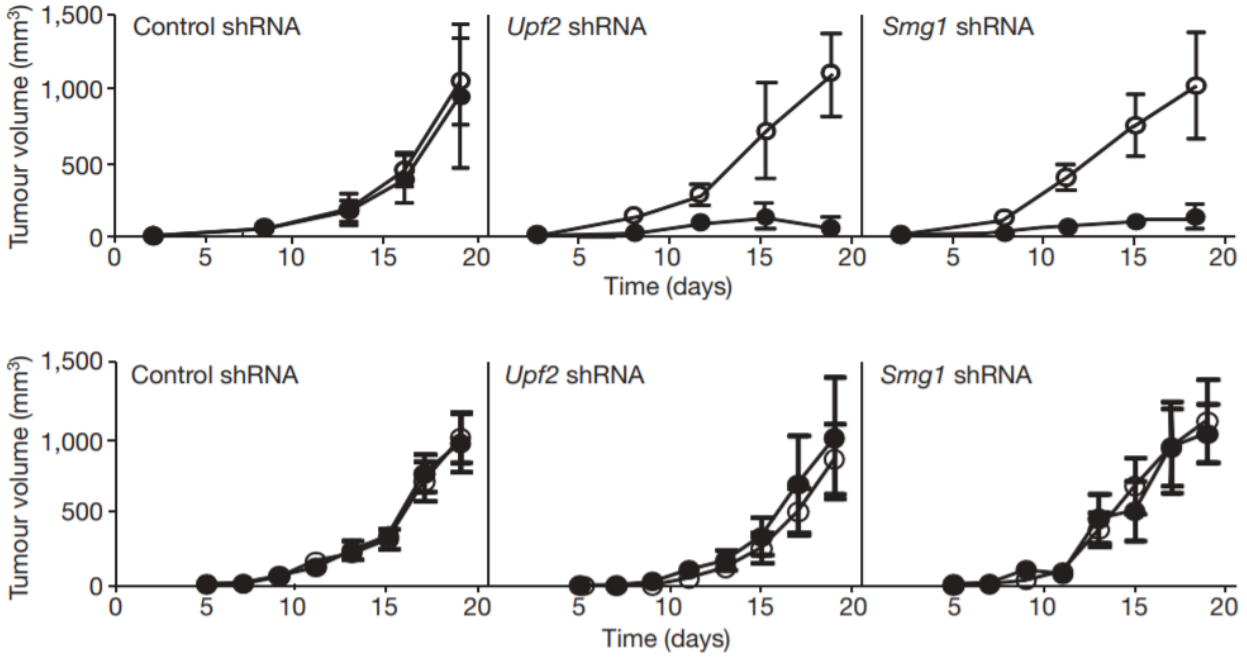
- Different method – predicting NMD from sequence position, not RNAseq

Lindeboom et al. 2019 **Nature Genetics**.

Pre-clinical evidence to support NMD from mouse studies:

Immune competent

Immune deficient



Preclinical evidence from Pastor et al. Nature

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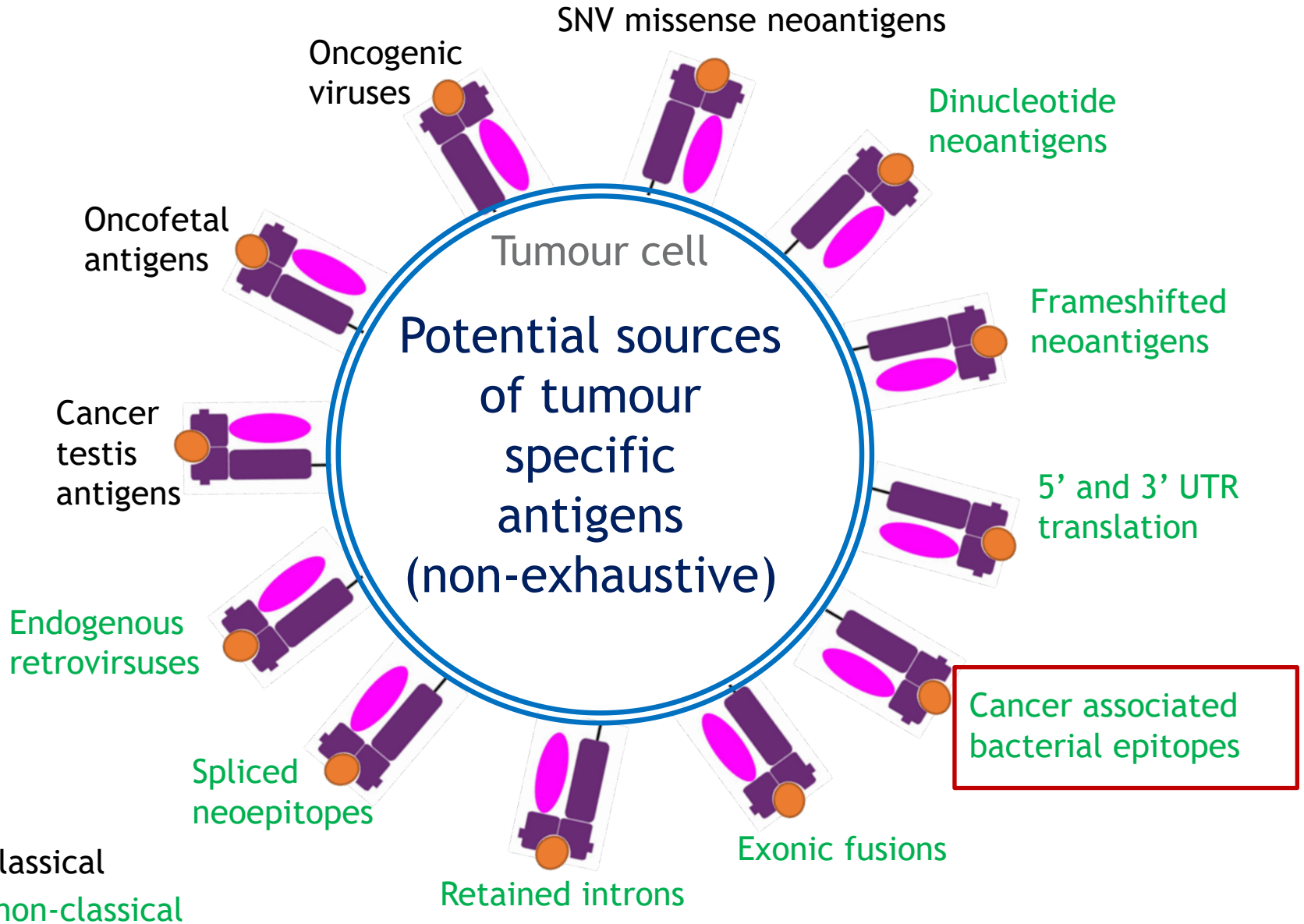

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Cancer associated bacteria - evidence of epitopes

nature

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nature › articles › article

Article | Published: 17 March 2021

Identification of bacteria-derived HLA-bound peptides in melanoma

Shelly Kalaora, Adi Nagler, [...]Yardena Samuels ✉

Nature **592**, 138–143 (2021) | Cite this article

25k Accesses | **11** Citations | **260** Altmetric | Metrics

- Recent evidence of HLA-bound bacterial epitopes in Melanoma

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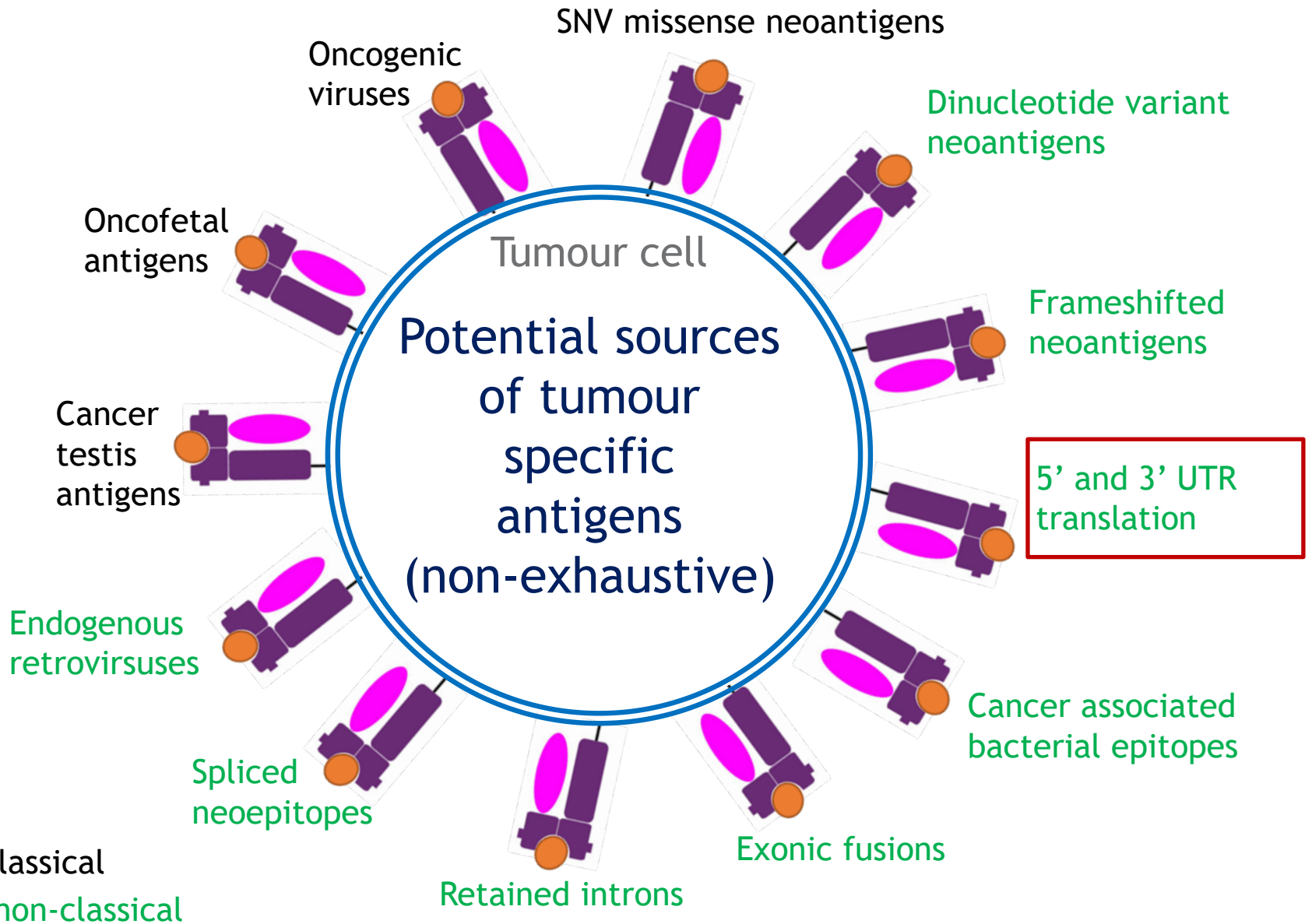

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Stop loss mutations causing 3’ UTR translation

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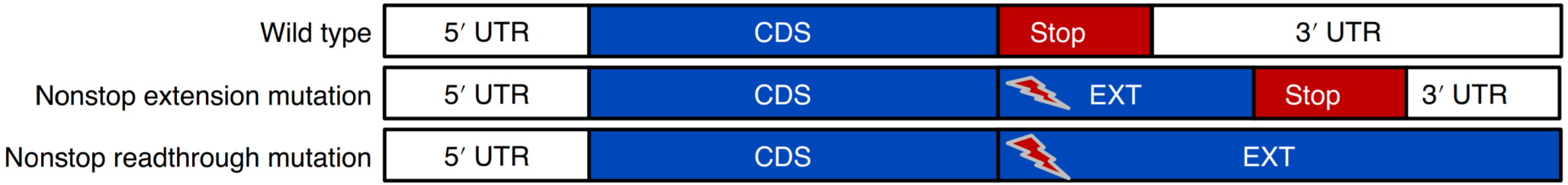
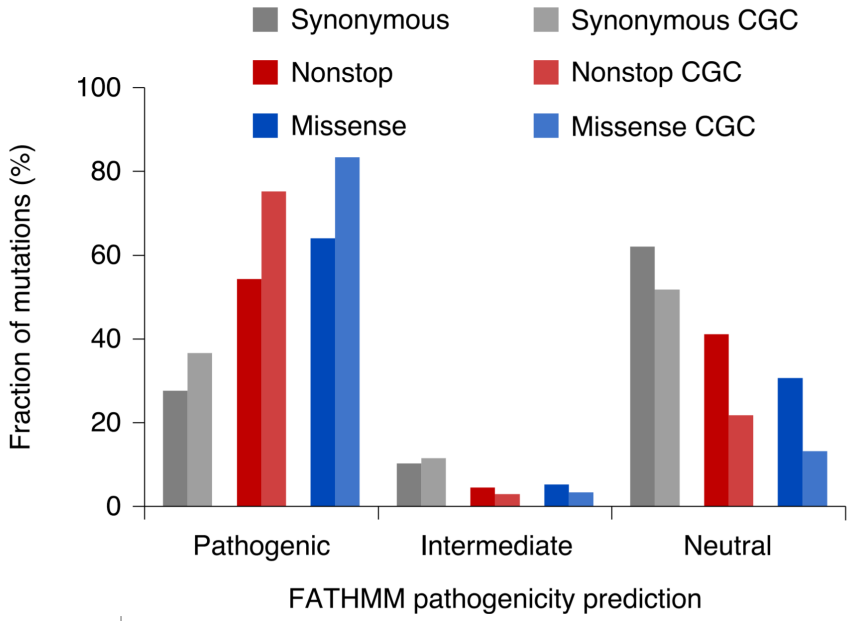
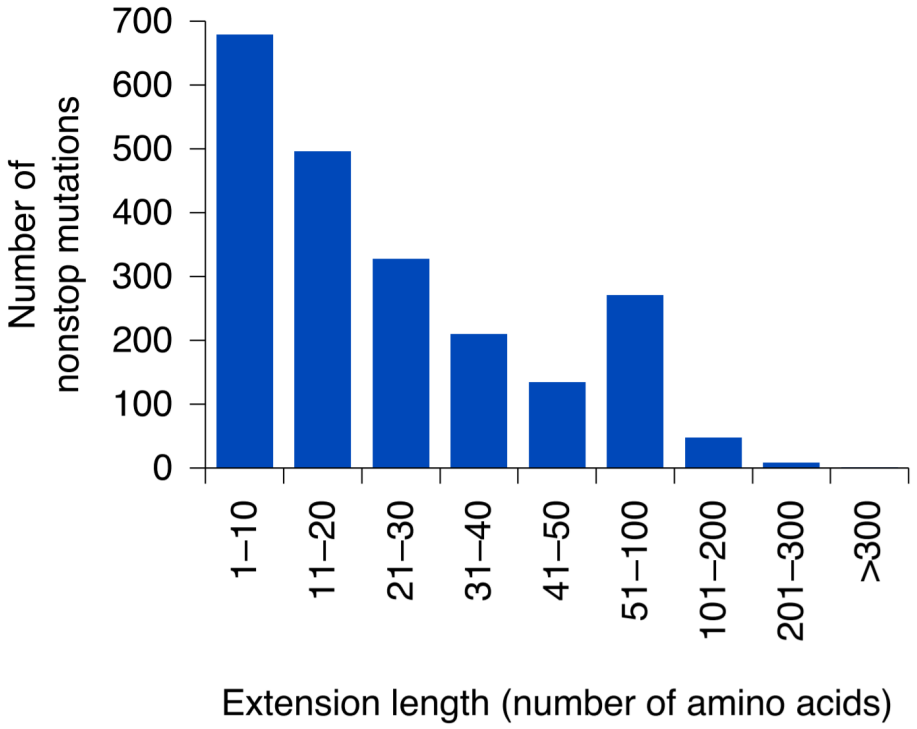




Article | Published: 27 July 2020

A pan-cancer analysis reveals nonstop extension mutations causing SMAD4 tumour suppressor degradation



Dhamija et al. Nature Cell Biology, 2020

Summary

- Complex set of biomarkers associated with CPI response – from our recent pan-can meta-analysis clonal TMB, CXCL9 and CXCL13 had strongest effect size
- Over half of the variance in response remains unexplained
- Non-classical epitope types may explain part of the missing variance
- Preliminary MANAFEST reactivity data supports non-classical epitopes as potential important drivers of immune response
- Strategies to generate more high quality epitopes may offer potential as a new immunotherapeutic approach, particularly in low-TMB cancers

TIGI Lab

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Shanila Fernandez Patel

Krupa Thakar

Marcellus Augustine

Alexander Coulton

Evie Fitzsimons

Chris SNG

Danwen Qian

Kelvin Tsang

Hongchang Fu

Ben Simpson

Royal Marsden Hospital

Samra Turajlic

James Larkin

The Francis Crick Institute

Charles Swanton

Samra Turajlic

Jeremy Carlton

MSKCC

Matthew D. Hellmann

UCL

Sergio Quezada

James Reading

Nicky McGranahan

We are also recruiting a postdoc data scientist working on an immuneoncology + machine learning role: k.litchfield@ucl.ac.uk

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